Gut microbiota as a target to limit toxic effects of traditional Chinese medicine: Implications for therapy

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ABSTRACT

Traditional Chinese medicines (TCMs) are medicines that are widely used in oriental countries under the guidance of ancient Chinese medicinal philosophies. With thousands of years of experiences in fighting against diseases, TCMs are gaining increasing importance in the world. Although the efficacy of TCMs is well recognized in clinic, the toxicity of TCMs has become a serious issue around the world in recent years. In general, the toxicity of TCMs is caused by the toxic medicinal compounds and contaminants in TCMs such as pesticides, herbicides, and heavy metals. Recent studies have demonstrated that gut microbiota can interact with TCMs and thus influence the toxicity of TCMs. However, there is no focused review on gut microbiota and the toxicity of TCMs. Here, we summarized the influences of the gut microbiota on the toxicity of medicinal compounds in TCMs and the corresponding mechanisms were offered. Then, we discussed the relationships between gut microbiota and the TCM contaminants. In addition, we discussed the methods of manipulating gut microbiota to reduce the toxicity of TCMs. At the end of this review, the perspectives on gut microbiota and the toxicity of TCMs were also discussed.

1. Introduction

Traditional Chinese medicines (TCMs) are medicines that are used under the guidance of ancient Chinese medicinal philosophies such as *Yin* and *Yang*. With the growing demands for natural medicines and the affordable costs, TCMs are gaining increasing importance in the world in recent years. However, the toxicity caused by TCMs has now become a serious issue both in and outside China [1,2]. A typical example is the drug-induced liver injury (DILI), a common adverse drug reaction that can lead to liver failure and even death. In China, the annual incidence of DILI is estimated to be 23.80 per 100,000 persons, and TCMs alone account for 26.81 % of those DILI cases [3]. Another example is the kidney failure induced by aristolochic acids, a series of herbal TCM compounds that are commonly distributed in plants of the genus *Aristolochia* and *Asarum* [4]. The kidney toxicity of these compounds has been reported in not only China, but also other countries such as Blgium, UK, France, and Japan [5]. In addition to the compounds that are endogenously synthesized by TCMs such as aristolochic acids, contaminants such as pesticides, herbicides, and heavy metals also contribute to the toxicity of TCMs [6,7]. The toxicities of TCMs mainly include hepatotoxicity, nephrotoxicity, cardiotoxicity, neurotoxicity and reproduction toxicity [8]. Because of the toxicity induced by TCMs, National Medical Products Administration has released several issues of notifications for the toxicity of TCMs [9].

Gut microbiota, also named as intestinal microbiota, is a group of microorganisms that live in the gastrointestinal tract of hosts in a mutualistic way. The human gut microbiota is composed of more than 2000 species, with the total number of bacterial cells 1–10 times more than that of human cells [10,11]. Studies over the past two decades have demonstrated that gut microbiota plays important roles in the maintenance of health and the development of diseases, such as non-alcoholic fatty liver disease, ulcerative colitis, Crohn's disease, diabetes and allergy [12]. Because of the importance of gut microbiota in development of disease, direct manipulation of gut microbiota such as fecal microbiota transplantation has been suggested in clinic to treat the diseases caused by gut microbiota disorder [13]. In addition, gut microbiota can metabolize drugs via synthesizing and releasing a series of enzymes. The metabolic capability of these enzymes is so strong that gut microbiota is regarded as an organ with the metabolic potential exceed that of the liver [14]. By transforming the administrated drugs, the gut microbiota can significantly influence the toxicity and efficacy of drugs [15]. For example, gut microbiota *β*-glucuronidases can activate the inactive irinotecan (SN-38 G) to active SN-38, a toxic compound toward epithelial cells, and finally lead to severe diarrhea in clinic [16]. In addition to direct metabolism, numerous studies have proved that gut microbiota can modulate the toxicity and efficacy of drugs in indirect mechanisms [17,18]. Understanding the molecular mechanisms behind the modulating effects of gut microbiota on drug toxicity and efficacy will help us to design appropriate therapeutic schedule and to improve the clinical response of patients to drugs.

Studies in recent years have shown that TCMs can interact with gut microbiota, and this interaction can enormously influence the toxicity and efficacy of TCMs. In our previous review, we and other groups have summarized the interactions between gut microbiota and TCMs, and the effects of gut microbiota on the therapeutic effects of TCMs [19–24]. However, no review has summarized the effects of gut microbiota on the toxicity of TCMs and the corresponding mechanisms. Focusing on the toxicity, here in this review we summarize the effects of gut microbiota on the toxicity of TCMs and the corresponding mechanisms. In addition, the possible approaches

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to control the toxicity of TCMs and perspectives on the related area are discussed.

2. Gut microbiota can interact with TCMs

Most TCMs are herbal medicines, although some TCMs may originate from fungi, minerals, and animals. One typical feature of herbal medicines is that many compounds of herbal medicines exhibit low bioavailability [25]. For example, the bioavailability of polyphenols, a group of compounds ubiquitously exist in herbal medicines, is usually less than 10 % [26]. Similarly, the bioavailability of ginsenosides, the major bioactive compounds of *Panax ginseng* C.A. Mey. and *Panax notoginseng* (Burk.) F.H. Chen, can be as low as 0.1 % [27]. Because of the low bioavailability, those compounds can pass through small intestine easily and reach colon, where the concentration of gut microbiota can be as high as 10^{12} cells per gram contents [28]. Thus, the unabsorbed compounds will inevitably contact and directly interact with gut microbiota. The direct interactions between gut microbiota and TCMs are bidirectional: on the one hand, the composition and function gut microbiota can be influenced by TCMs; on the other hand, the compounds of TCMs can be metabolized by gut microbiota. In addition to direct reactions, indirect reactions can happen between TCMs and gut microbiota. In this type of reaction, the immune and metabolic system of host act as a bridge that connecting the two ends. The immune system of gastrointestinal tract can synthesis and release a series of materials with the capability to modulate the composition of gut microbiota, such as immunoglobulin A and other antimicrobial peptides [29,30]. The absorbed TCMs can modulate the immune system of gastrointestinal tract, and finally lead to the compositional change of gut microbiota. For example, farrerol, a TCM compound isolated from genus *Rhododendron*, can change the expression of antimicrobial peptides in bovine mammary epithelial cells and thus enhance the defense against *Staphylococcus aureus* infection [31].The direct and indirect interactions between gut microbiota and TCMs can remarkably modify the toxicity of TCMs.

3. Gut microbiota and the toxicity of TCM compounds

3.1. Gut microbiota direct metabolism of TCM compounds

Gut microbiota can synthesis and release a series of enzymes with the capability to metabolize xenobiotics (the compounds that are foreign to hosts such as dietary components, environmental pollutants, and pharmaceuticals). Those enzymes such as *β*-glucuronidase, *β*-glucosidase, *β*-galactosidase, nitroreductase, *α*-rhamnosidase, and *β*-xylosidase can transform the compounds of TCMs [32], and thus directly modify the toxicity of TCMs. The direct modifications include increasing and decreasing the toxicity, detoxification, and activation of toxicity (Fig. 1).

3.1.1. Increasing the toxicity

Amygdalin is a compound that is found in *Armeniacae Amarae Semen*, a TCM that is widely used to treat respiratory system disease such as bronchitis, emphysema. The toxicity of *Armeniacae Amarae Semen* that is manifested as nausea, emesis, chest distress, dizziness, and even death is reported repeatedly in clinic [33]. Amygdalin was applied as an agent to treat cancer in the 1960s although later clinical study demonstrated no improvements in both survival and symptoms [34]. In human, the maximum tolerance dose of intravenous injection is 5 g (approximately 0.07 g/kg) [35]. Studies have found out that amygdalin

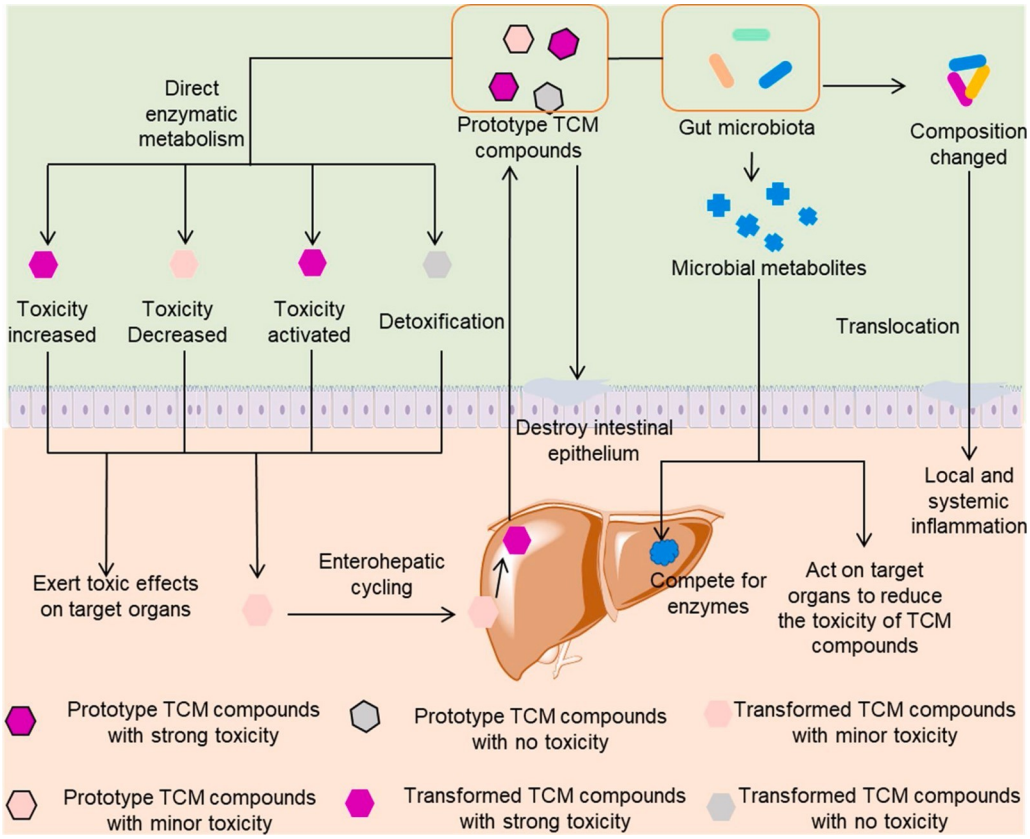

Fig. 1. The effects of gut microbiota on the toxicity of traditional Chinese medicines (TCMs) and corresponding mechanisms.

is responsible for the toxicity of *Armeniacae Amarae Semen* and gut microbiota plays significant role in modification of the toxicity of amygdalin. In an animal study, the conventional rats receiving amygdalin at 600 mg/kg showed poisonous symptoms including lethargy and convulsions, while germ-free rats receiving same dosage did not exhibit conspicuous poisonous symptoms [36]. In addition, the conventional rats showed lower recovery of amygdalin than that of germ-free rats when both groups received a non-toxic oral dose at 50 mg/kg, and fecal amygdalin were detected only in germ-free rats [36]. This study suggested that gut microbiota is involved in the metabolism and toxicity of amygdalin. Further studies showed that gut microbiota can hydrolyze the glycosidic linkage of amygdalin and thus release mandelonitrile, a compound that can spontaneously breaks down to generate benzaldehyde and toxic prussic acid [36,37]. Those studies demonstrated the toxicity increasing effects of gut microbiota on amygdalin. In addition to amygdalin, other compounds from TCMs such as arbutin and puerarin can be metabolized by gut microbiota and produce metabolites with stronger toxicity (Table 1).

Enterohepatic circulation also plays important role in the toxicity of TCMs. Irinotecan (also known as CPT-11), is an intravenous chemotherapeutic drug that is structurally modified from the alkaloid of *Camptotheca acuminate*. In clinic, more than 40 % of patients that undergo CPT-11 therapy can present with severe diarrhea, resulting in reduction of dosage or termination of the drug [38]. After injection, CPT-11 can undergo a series of biotransformation in the liver: carboxylesterases first convert CPT-11 to nuclear topoisomerase 1 enzyme inhibitor SN-38, and UDP-glucuronosyltransferase then convert SN-38 to its inactive form SN-38 G [39]. When passed through biliary duct into intestine, SN-38 G can be converted back to SN-38 by gut microbiota. SN-38 is a toxic compound on epithelial cells and is responsible for the diarrhea in patients with receiving CPT-11. Meanwhile, CPT-11 treatment can lead to dose dependent modification of gut microbiota such as *Lactobacillus*, *Bacteroides spp.*, and *Bifidobacterium* [40]. Furthermore, treatment with antibiotics can reduce the severity of CPT-11-induced diarrhea and the cecum injury [41]. Those studies demonstrated that gut microbiota and enterohepatic circulation can modify the toxicity of TCM compounds.

3.1.2. Decreasing the toxicity

Direct metabolism may also lead to decreasing of the toxicity of TCM compounds. The lateral roots of *Aconitum carmichaeli* Debx (Fuzi) is a TCM that is widely used to treat heart failure in clinics, but often cause toxic effects on nervous and cardiovascular systems and even lead to death [42]. Aconitum alkaloids are the major compounds that are responsible for the pharmacological activity and toxicity of Fuzi. In clinic, Fuzi is usually processed by boiling for hours to reduce the toxicity before being prescribed to patients. In this process, diester-diterpenoid alkaloids can be degraded into products with the same strength in pharmacological effect, including the monoester-diterpenoid alkaloids, and nonester-diterpenoid alkaloids [43,44]. The median lethal dose (LD_{50}) for single oral dose of aconitine is 1.0–1.8 mg/kg in mice, while the LD_{50} for of monoester-diterpenoid alkaloids including benzoylaconine, benzoylmesaconin, and benzoylhypaconine is 1.50, 0.81, and 0.83 g/kg, respectively [45]. Thus, the toxicity of Fuzi is significantly reduced in the process of boiling. In the gastrointestinal tract, gut microbiota can transform aconitum alkaloids in a similar way through deacylation, and esterification, and removal of methyl hydroxyl [46,47]. As a result, the gut microbiota reduces the toxicity of Fuzi. However, the extent of this reduction is limited as evidenced by the fact that oral administration of large dose of raw Fuzi can cause acute toxicity and even death [48]. In addition to aconitine, other TCM compounds including butyl paraben and baicalin can be transformed by gut microbiota into less toxic compounds (Table 1).

3.1.3. Detoxification

In addition to modification of the strength of the toxicity, gut microbiota can transform the active TCM compounds into inactive products and thus detoxify TCMs. Digoxin is a cardiac glycoside that is originally separated from *Digitalis purpurea* (foxglove) with the capability to inhibit the Na^+/K^+ ATPases in cardiocytes. Because of the strikingly narrow therapeutic window, the use of digoxin in clinic require careful monitoring to prevent the possible cardiotoxicity. In more than 10 % patients, a significant high level of digoxin is transformed to a cardio-inactive product-dihydrodigoxin, through the reduction of α,β-unsaturated lactone ring [49]. Early study suggested that the gut microbiota is involved in this process of inactivation because coadminstration of digoxin with antibiotics saliently reduced the production of dihydrodigoxin [49]. Recent studies demonstrated that digoxin can conspicuously induce the activity of a “cardiac glycoside reductase” (cgr) operon, a cytochrome-encoding operon that is specific to drug-metabolizing strains of *Eggerthella lenta* [50,51]. Quantitative study showed that this type of transformation by gut microbiota can lead to final inactivation of more than 50 % of the administered digoxin [52], and thus significantly impacts the clinic use of this drug. Oxalate is an herbal compound that exists in many TCMs with the ability to induce hyperoxaluria, kidney stones, and cardiac conduction disorders [53–55]. Besides digoxin, gut microbiota can detoxify this compound with the help of formyl-CoA transferase and oxalyl-CoA decarboxylase (Table 1).

3.1.4. Activation of toxicity

In contrast to detoxification of TCMs, activation of toxicity by gut microbiota can transform the nontoxic compounds into toxic compounds. Cycasin is an azoxyglucoside present in plants of family *Cycadaceae* with hepatotoxic and carcinogenic ability. Studies have demonstrated that gut microbiota plays important role in activation of the toxicity of cycasin. In germ-free mice, consecutive administration of cycasin for 20 days at large dose did not induce conspicuous toxicity by checking the body weight, food intake, and the appearance of tissues at microscopic level.

In contrast, the conventional rats showed significant reduction of food intake and body weight, a high mortality, and severe live necrosis [56]. Later studies showed that gut microbiota can transform cycasin into its aglycone (methylazoxymethanol), the aglycone can be further transformed into diazomethane, a toxic compound with hepatotoxic and carcinogenic effects [57].

3.2. TCMs directly modulate the composition and metabolism of gut microbiota

Direct contact between TCMs and gut microbiota can lead to not only the transformation of TCM compounds but also the compositional and metabolomic change of gut microbiota, which further impact on the toxicity of TCMs. In normal condition, gut microbiota harbor a large number of microbial species including opportunistic bacteria, pathogenic bacteria and probiotics that stay in a homeostasis. Those bacteria synthesis and release a series of metabolites such as short-chain fatty acids, indole derivatives, polyamines, vitamins [58,59]. Those metabolites are helpful for hosts to maintain intestinal barrier function, regulate lipid metabolism and glucose homeostasis, modulate immune system, etc. On the contrary, the disturbed gut microbiota contribute greatly to the development of diseases such as diabetes, ulcerative colitis, colorectal cancer, and Parkinson's disease [60,61]. In addition, the

Table 1
Roles of gut microbiota on the toxicity of TCMs.

Compounds	Types of mechanism	Models for Ref. mechanisms	Toxicity interactions models (indicators)	Major bacterial species evaluation	Influence on involved toxicity	Specific	
Baicalin	Direct metabolism	Human fecal suspension	HepG2 cells	Not mentioned	Decreasing the toxicity	Gut microbiota transforms baicalin to baicalein, a compound with less toxicity on HepG2 cells	[143]
Aconitine	Direct metabolism	Human fecal suspension	Normal rats	*Bacteroides fragilis*, *Klebsiella pneumoniae*, *Clostridium butyicum*	Decreasing the toxicity	Gut microbiota transforms aconitine to metabolites with less cardiotoxicity, including benzoyldeoxyaconin and lipoaconitine	[44, 46, 47]
Butylparaben	Direct metabolism	Human fecal suspension	HepG2 cells	Not mentioned	Decreasing the toxicity	Gut microbiota transforms butyl paraben to *p*-hydroxybenzoic acid, a compound with less toxicity on HepG2 cells	[144]
Geniposide	Direct metabolism	Human fecal suspension, gut bacteria *Bifidobacterium longu*m HY8001 and *Bacteroides fragilis*, and microbial enzyme mix	HepG2 cells	*Bifidobacterium longum* HY8001, *Bacteroides fragilis*	Increasing the toxicity	Gut microbiota transforms geniposide to genipin, a compound with stronger toxicity on HepG2 cells	[145]
Amygdalin	Direct metabolism	Conventional and germfree rats	Conventional and germfree rats	Not mentioned	Increasing the toxicity	Gut microbiota metabolizes amygdalin to benzaldehyde, glucose and highly toxic hydrogen cyanide	[36, 146]
Arbutin	Direct metabolism	Human fecal suspension	HepG2 cells	Not mentioned	Increasing the toxicity	Gut microbiota metabolizes arbutin to hydroquinone, a metabolite with stronger toxicity	[147]
Puerarin	Direct metabolism	Human fecal suspension	Tumor cell lines P388, SNU C4, A549, and ZR-75− 1	*Peptostreptococcus spp.* (Y- 10)	Increasing the toxicity	Gut microbiota metabolizes puerarin to daidzin and calycosin, metabolites with stronger toxicity	[148]
Daidzin	Direct metabolism	Human fecal suspension	Tumor cell lines P388, SNU C4, A549, and ZR-75− 1	*Bifidobacterium spp.* (K-111)	Increasing the toxicity	Gut microbiota metabolizes daidzin to dadizein and calycosin, metabolites with stronger toxicity	[148]
Irinotecan (CPT-11)	Direct metabolism and enterohepatic circulation	Germ-free and holoxenic mice	Germ-free and holoxenic mice	*Escherichia coli*	Increasing the toxicity	Liver transform CPT-11 to bioactive SN-38, and then to inactive SN-38 G. Gut microbiota convert the intestinal SN-38 G back to SN-38, a metabolites toxic to epithelial cells	[16, 149]
Digoxin	Direct metabolism	Human subjects, culture-based assays and gnotobiotic mice	Digoxin concentration	Gut Actinobacterium *Eggerthella lenta* expressing cardiac glycoside reductase operon	Detoxification	*Eggerthella lenta* carrying cardiac glycoside reductase operon convert digoxin to cardio-inactive dihydrodigoxin	[49, 51, 52]
Oxalate	Direct metabolism	Healthy human subjects, subjects undergone jejunoileal bypass	Oxalate concentration	*Oxalobacter formigenes*	Detoxification	Gut bacteria such as Oxalobacter formigenes use oxalate as a sole carbon source and converts oxalate to oxalyl-	[150, 151, 152]

		surgery, human fecal samples, rats, mice				CoA and formyl-CoA	
Cycasin	Direct metabolism	Germfree rats and gnotobiotic rats	Liver injury of rats	*Streptococcus fecalis*, *Lactobacillus salivarius salicinius*	Activation of toxicity	Gut microbiota transforms nontoxic cycasin to toxic methylazoxymethanol and diazomethane	[56, 57]
Triptolide	Modulation of gut microbiota	Conventional mice and conventional mice treated with antibiotics	Liver injury of mice	Not mentioned	Decreasing the toxicity	Gut microbiota produced propionate ameliorate the liver injury induced by triptolide	[65]
Arsenic	Direct metabolism, modulation of gut microbiota,	Conventional mice, antibiotic-treated and germ-free mice, simulator of the human intestinal microbial ecosystem	Mortality of mice, bioavailability of arsenic	*Faecalibacterium prausnitzii*	Different study showed different increasing/ decreasing effects on toxicity	Gut microbiota transforms arsenite to monomethylarsonic acid, monomethylarsonous acid and monomethylmonothioarsonic acid; arsenic disrupt the structure of intestinal epithelium and thus enables the translocation of gut microbiota and cause systemic inflammation; arsenic disrupt the composition and metabolism of gut microbiota	[81, 83, 84, 153]
Mercury							

(*continued on next page*)

Table 1 (*continued*)

Compounds	Types of mechanisms	Models for interactions	Toxicity evaluation models (indicators)	Major bacterial species involved	Influence on toxicity	Specific mechanism	Ref.
	Direct metabolism	Aquatic organisms, terrestrial invertebrates, mammals, fecal specimen, intestinal contents, and the isolated intestinal microbes	Invertebrates and mammals, bioavailability of arsenic	*Desulfovibrio spp.*, *Desulfovibrio piger*, *Desulfovibrio giganteus*, *Desulfovibrio termitidis*, *Desulfotomaculum ruminis*, *Desulfobulbus propionicus*, and two enrichment cultures Zy1 and EF4 from *Eisenia foetida*	Increasing the toxicity	Gut microbiota transform inorganic mercury to methylmercury, a compound that can easily cross the biological barriers such as blood-brain barrier	[154, 155]

synthesis and release of metabolites by gut microbiota would be changed, which further accelerate the development of disease. For example, the elevated level of trimethylamine-*N*-oxide contribute to the development of cardiovascular diseases, such as myocardial infarction and stroke [62]. TCMs can directly modulate the composition and metabolism of gut microbiota, and thus further influence the toxicity of TCMs.

Tripterygium wilfordii Hook. f. is an herbal medicine that is widely used for treatment of rheumatoid arthritis [63]. However, it can also cause gastrointestinal, immune and reproductive toxicity that can manifested as diarrhea, leukopenia, thrombocytopenia, rash, and malfunction of reproductive system [63]. Triptolide is one of the major bioactive compounds isolated from *Tripterygium wilfordii* Hook. f. with the activity of anti-inflammation, immune modulation, anti-proliferative and proapoptotic activity [64]. Even though it has been used to treat inflammatory diseases and autoimmune diseases, clinical use of it is limited because of severe toxicity, particularly liver injury. A recent study showed that the perturbation of gut microbiota is associated with triptolide-induced hepatotoxicity [65].

Antibiotic-induced depletion of gut microbiota can significantly aggravate the liver injury and even lead to mortality when a safe dosage of triptolide is administrated at 0.5 mg/kg, and this process is accompanied by dramatically elevation of long-chain fatty acids. Propionate is one type of short-chain fatty acids that are produced by gut microbiota [20]. Administration of propionate ameliorated triptolide-induced hepatotoxicity, and this process is associated with decrease of long-chain fatty acids in liver [65]. This study showed that gut microbiota produced propionate is can reduce the liver toxicity caused by triptolide.

3.3. Indirect reactions

In addition to direction reactions, the toxicity of TCMs can be indirectly influenced by gut microbiota. This type of indirect reaction usually involves the metabolic system and the immune system of hosts. The indirect reaction involving immune system will be discussed in the following sub-section, and here we only discuss the indirect reaction involving metabolomic system. The impact of gut and liver metabolism on the toxicity of chemical drugs has been well studied in the cases of acetaminophen, a drug that can cause severe and even fatal hepatotoxicity. In the liver, acetaminophen can be metabolized to toxic compound *N*-acetyl-*p*-benzoquinone imine and inactive compounds acetaminophen sulfate and acetaminophen glucuronide [66]. *p*-cresol, a microbial product that is produced during the metabolism of tyrosine and phenylalanine, can compete for cytosolic sulfotransferase 1A1 in the liver. This competition between *p*-cresol and acetaminophen reduces the ability of hosts to detoxify acetaminophen [67]. Although this type of

indirect reaction has not been well proved in TCMs, several studies have implied the existence of this type of reaction between gut microbiota and TCMs. For example, a toxic herbal medicine Lang-du (the roots of *Euphorbia fischeriana* Steud) can increase the level of *p*-cresol and *p*-cresol sulfate in the blood [68]. Considering that *p*-cresol can influence the detoxifying capability of liver, it can be inferred that the gut microbiota might enhance the toxicity of Lang-du by competing for enzymes metabolizing toxic compounds in Lang-du, such as jolkinolides A and B. The liver highly express cytochrome P450 enzymes, a set of enzymes that can contribute to the phase I metabolism of 75 % of known pharmaceuticals [69]. Gut microbiota can transform TCM compounds such as naturally occurring ginsenosides, a class of compounds showing no inhibiting effects on cytochrome P450 enzymes, to metabolites with the ability to inhibit the cytochrome P450 enzymes [70]. Thus, the toxicity of other compounds could be influenced.

3.4. Complex reactions

We have discussed single mechanisms that influence the toxicity of TCMs, however, in many cases the interactions between TCMs and gut microbiota involves multiple mechanisms. The complex reactions include modification of gut microbiota composition and metabolism, metabolism of TCMs, and changing the immune system of hosts. And those mechanisms can influence the toxicity of TCMs simultaneously. A healthy composition of gut microbiota exhibits conspicuous role in fighting against the invasion of pathogens, maintaining the integrity of epithelial barrier, modulating the metabolism of hosts, shaping the innate and adaptive immune responses, affecting the cognitive function [71–74]. On the contrary, dysbiosis of gut microbiota contribute to the development of a battery of diseases that include, but not limited to, inflammatory bowel disease, colorectal cancer, allergy, metabolic syndrome, cardiovascular disease [60,75]. The gastrointestinal epithelium is mainly made up of five types of cells: absorptive enterocytes, goblet cells, Paneth cells, enteroendocrine cells and M cells. Equipped with those cells, the gastrointestinal immune system has evolved to confine the gut microbiota and maintain the symbiotic relationship between host and gut microbiota. When gastrointestinal epithelium is breached, the materials such as lipopolysaccharides released by gut microbiota can enter blood and trigger local or systemic inflammation [76].

Arsenic is a heavy metal medicine that is widely used in TCMs and ancient Greek and Roman medicine to leukemia, syphilis and myeloma, however, it also lead to cardiac disorder, respiratory failure, hypokalemia, cerebral infarction, and even death in clinic [77,78]. The arsenic can present in different methylation levels (monomethyl, dimethyl, or trimethyl) and oxidoreduction states (trivalent or pentavalent). The methylation levels and oxidoreduction states of arsenic significantly impact on the toxicity of arsenic in mammals. *in vitro* and *in vivo* studies have demonstrated that gut microbiota can directly metabolize arsenic by oxidative methylation and glutathione conjugation, two processes that can also change the bioavailability of arsenic [79,80]. As a result, the toxicity of arsenic is significantly influenced. In addition to direct metabolism by gut microbiota, arsenic can change the composition of gut microbiota and thus further influence the metabolism of gut microbiota, leading to significant content change of gut microbiota metabolites such as bile acids and amino acids [81]. The study suggests that modulation of the composition and metabolism of gut microbiota may also influence the toxicity of arsenic. Furthermore, arsenic can directly disrupt the structure of intestinal epithelium, enabling the translocation of gut microbiota and gut microbiota metabolites, and finally lead to increase of endotoxemia and local and systemic inflammation response [82,83]. Taken together, those studies indicated that the complex reactions including direct metabolism by gut microbiota, changing the composition and metabolism of gut microbiota, and disturbing host's immune system can significantly influence the toxicity of arsenic. However, while most studies showed that gut microbiota can exacerbate arsenic toxicity, one recent study using antibiotic-treated, transgenic, germ-free, and gnotobiotic animal models demonstrated

Table 2

Typical TCM contaminants and their roles on gut

Types of contaminants	Names	Experimental Models	exposure conditions	Outcomes	Refs.
Insecticides	Chlorpyrifos	Mice	Daily dose at 1 mg/kg for 30 days	Increased *Bacteroidetes* and decreased *Firmicutes*, altered urine metabolites, lead to intestinal inflammation and abnormal intestinal permeability	[156]
	Monocrotophos	BALB/c Mice	Daily dose at 28 μg/kg for 180 days	Gut microbial organophosphate degradation produces SCFAs such acetic acid, which induces gluconeogenesis and thereby lead to glucose intolerance	[157]
	Diazinon	C57BL/6 mice	In drinking water at 4 ppm for a period of 13 weeks	Altered quorum sensing systems of gut bacteria, and lead to the regulation of downstream genes and pathways. It also shows sex difference on gut bacteria, for exampole, *Lachnospiraceae_Johnsonella* was reduced –16-fold in male mice but increased +1.8-fold in female animals	[158, 159]
	Organochlorine pesticides	C57BL/6 mice	Oral gavage p,p'-DDE (1 mg/kg bw/day) or *β*-HCH (10 mg/kg bw/ day) for 8 weeks	Remodeled gut bacteria responsible for bile salt de-conjugation and dihydroxylation, typically decreased *Parabacteroides*, *Prevotella*, *Bacteroides*, *Clostridium XlVa* and *Clostridium IV*, increased *Barnesiella*, *Alloprevotella*, *Oscillibacter*, *Lactobacillus*, *Parasutterella* and *Akkermansia*, and thus led to disorders of entero- hepatic bile acid metabolism	[160]
Herbicide	Pentachlorophenol	Goldfish	0–100 μg/L pentachlorophenol for 28 days	Body weight and liver weight were reduced, and hepatic CAT and SOD activities were inhibited, *Bacteroidetes* and *Bacteroides* abundance, and *Firmicutes*/*Bacteroidetes* ratio were associated with phenotypes	[161]
	Glyphosate	Chinese mitten crab	Exposure to glyphosate (48.95 mg/ L) for 96 h	Reduced the survival rate of crabs, negatively influence the antioxidant capacity and digestive enzyme activity, increased *Proteobactria* and *Bacteroidetes*	[162]
Fungicides	Carbendazim	C57BL/6 mice	0.2, 1, and 5 mg/kg body weight for 14 weeks	Increased body, liver, and epididymal fat weight, decreased *Bacteroidetes*, *Verrucomicrobia* and increased *Actinobacteria*, altered the production of short-chain fatty acids	[163]
	Imazalil	C57BL/6 mice	0.1, 0.5, and 2.5 mg/kg body weight for 2, 5, or 15 weeks	Disturbed the intestinal barrier function, reduced mucus secretion, decreased the expression of cystic fibrosis transmembrane conductance regulator-related genes, decreased S24− 7, *Prevotella*, *Bacteroidetes*, *Parabacteroides*, and increased *Clostridiales*, *Oscillospira* and *Helicobacteraceae*	[164]
	Propamocarb	ICR mice	3, 30, and 300 mg/L in drinking water for a duration of 28 days.	Disturbed transcription of hepatic genes related to lipid metabolism, induced gut microbiota dysbiosis, perturbed fecal metabolites including succinate, SCFAs, bile acids and trimethylamine, decreased *Oscillospira*, *Parabacteroides*, *Desulfovibrio* and *Ruminococcus*, and increased *Bacteroides*, *Dehalobacterium* and *Butyricimonas* in cecal contents	[165]
	Epoxiconazole	SD Rat	0, 4 and 100 mg/kg/day for 90 days	Decreased serum levels of total bilirubin, cholesterol and cholinesterase, increased glucose levels, increased *Proteobacteria* and *Bacteroidetes*, and decreased *Firmicutes*	[166]
Heavy metals	Cadmium	Balb/c mice	20 and 100 mg/kg cadmium chloride for 3 weeks	Decreased the population of *Bifidobacteria* and *Lactobacilli*, reduced the thickness of mice inner mucus layer, lowered key genes involved in SCFAs production	[167]
	Chromium	*Bufo gargarizans* tadpoles	0, 13, 104, and 416 mg Cr^{6+} L^{-1} for about 70 days	Altered intestinal tissue structure; declined the body length, body wet weight, intestinal length and wet weight; decreased *Porphyromonadaceae*, *Aeromonas*, *Dechloromonas* and increased *Citrobacter*	[168]
Mycotoxin	Aflatoxin B1	Pacific white shrimp	5 ppm aflatoxin B1 for 30 days	Increased intestinal and hepatopancreas activities of superoxide dismutase, catalase, glutathione peroxidase; increased *Proteobacteria* and *Firmicutes*, and decreased *Bacteroidetes*	[169]
	Ochratoxin A	Peking ducklings	235 μg/kg body weight for two weeks	Increased the relative abundance of lipopolysaccharides-producing *Bacteroides*, induced the accumulation of lipopolysaccharides and inflammation in the liver	[170]
	Zearalenone	Rats	0, 0.2, 1.0 and 5.0 mg/kg bw by gavage for 4 weeks	Impaired gut morphology, induced inflammatory reaction, decreased mucin expression, increased intestinal permeability, decreased TJ proteins and activated RhoA/ROCK pathway, increased the abundances of *Bacteroidetes* yet with no statical significance	[171]

microbiota and hosts.

that gut microbiota can mitigate arsenic toxicity [84]. Thus, further studies are needed to clarify whether gut microbiota can increase arsenic toxicity or not.

4. Combination of TCMs (compatibility) and the toxicity of TCMs

Different from modern drugs that each of them is designed for a specific target, TCMs are usually used in combination to target multiple targets. The combination of TCMs (which is also known as Compatibility, or Peiwu) is an ancient art aimed for increasing the efficacy and lowering the toxicity of TCMs [85]. Ancient TCM practitioners found out

that combinational use of some TCMs will lead to significant side effects. They summarized those TCMs and generalized them as the theory "incompatibility" (Xiangfan) and "eighteen incompatible medicaments" (Shibafan) to forbid the TCM practitioners to combine those TCMs. Although these theories have been practiced in China for thousands of years, their mechanisms remain unknown for a long time. Gansui (the roots of *Euphorbia kansui* T.P. Wang) and Gancao (the roots and rhizomes of *Glycyrrhiza uralensis* Fisch.) are two typical TCMs that belong to "eighteen incompatible medicaments" [86]. Although Gancao-Gansui combination did not cause conspicuous histopathologic damage on gastrointestinal tract tissue, this combination caused gut microbiota dysbiosis [86]. Metagenomics and fecal lipid metabolomics showed that Gancao-Gansui combination disturbed lipid metabolism. This study partly proved the rationality of the theory "incompatibility" and "eighteen incompatible medicaments", and that gut microbiota is involved in toxicity-enhancing effects TCMs combination. On the contrary, another study showed that gut microbiota is involved in the toxicity-reducing effects of TCMs combination. Badou (the degreased powder of the fruits of *Croton tiglium* L.) is a TCM with strong gastrointestinal toxicity, and its toxicity is partly associated with gut microbiota. However, when it is combined with Dazao (the fruits of *Ziziphus jujuba* Mill.), its toxicity is significantly reduced and the gut microbiota dysbiosis is partly restored [87]. Although those two examples demonstrated that gut microbiota is involved in the toxicity enhancing and toxicity reducing effects of combinational use of TCMs, the two examples just give us associative relationship but not causal relationship between altered toxicity of TCMs and gut microbiota. Thus, more studies are needed to verify the relationship between the toxicity of TCMs and gut microbiota.

5. Gut microbiota and toxicity of contaminants

Contamination is one important factor that lead to the toxicity of TCMs, especially herbal medicines. The common contaminations include pesticides, herbicides, heavy metals, fungal/microbial contamination, pollens, dust, insects, parasites, prescription drugs [88–90]. Gut microbiota have been demonstrated to be involved in the toxic mechanism of some of these contaminations, especially mycotoxins, pesticides and heavy metals (Table 2). So far, more than 40 mycotoxins such phomopsins and sterigmatocystin have been detected in herbal medicines [91]. The typical mycotoxin is patulin, a compound that bears polyketide lactone structure and can induce gastrointestinal, neurological, and immunological adverse effects [92]. In addition to direct cytotoxicity, disruption of the gut barrier and induction of bacterial translocation are the other mechanisms by which patulin exert its toxicity [93]. The use of pesticides and herbicides is very common in plantation and storing of herbal medicines, especially in developing countries. Most pesticides remain chemically stable during the growing, harvesting and processing of herbal medicines, and thus the contents of pesticides in final products of herbal medicines can surpass the limitations stipulated in pharmacopeia. Studies have demonstrated that induction of gut microbiota dysbiosis by pesticides is quite common and can lead to various adverse effects on hosts [94]. For example, chlorpyrifos induces the broken of the integrity of gut barrier, leading to the increased entrance of lipopolysaccharide into hosts and low-grade inflammation [95]. With the development of global economy, pollution of arable land by heavy metals including mercury, cadmium, lead, chromium, and arsenic has become an important issue [96]. Gut microbiota can change the bioavailability of heavy metals via sulfonation, methylation, oxidization, or reduction [97–99], and thus direct influence the toxicity of heavy metals. Heavy metal such as cadmium can also interact with the host's immune system and composition and metabolism of gut microbiota, and thus the toxicity of heavy metals can be changed [100].

6. Targeting gut microbiota to reduce the toxicity of TCMs

Because of the important roles of gut microbiota in modulation of the toxicity of TCMs, targeting gut microbiota has emerged as a new frontier to manipulate the toxicity of TCMs. Here we summarized the possible ways targeting gut microbiota to reduce the toxicity of TCMs (Fig. 2).

6.1. Processing

Unlike other ethno-herbal medicines that are usually used in simply fresh or dried from, many TCMs are subjected to specific treatments such as boiling, streaming and frying before they are used in clinic or in manufacturing TCMs. Those treatments are usually referred to as "processing", and this processing is different from the procedure of manufacturing or preparation the TCMs [101]. Processing has been practiced for enhancing the efficacy and lowering the toxicity of TCMs for thousands of years. The mechanisms of efficacy enhancing and toxicity lowering effects of processing is important issue in modernization of TCMs. Studies have demonstrated that processing such as boiling can transform the toxic compounds to nontoxic or less toxic compounds and thus change the toxicity of TCMs by, as is in the case of Aconitum roots [102]. In recent years, researchers have demonstrated that processing can influence the gut microbiota and thus influence the pharmacological effects of TCMs [103].

Guisui is a toxic TCM used for treatment of edema, ascites and asthma. Because of the strong toxicity such as hepatic and gastrointestinal toxicity, it is usually fry-baked with vinegar reduce the toxicity. However, the mechanism of the toxicity-reducing effects of fry-baked with vinegar is known. A recent study showed that vinegar processed Gansui significantly reduced 10 toxic compounds in Gansui, such as kansuinin B, kansuinin C and kansuinin E [104]. Meanwhile, 16 S rDNA microbial community analysis showed that vinegar processed Gansui can significantly modify the composition of gut microbiota in comparison with Gansui group. Furthermore, fecal metabolomics showed that vinegar processed

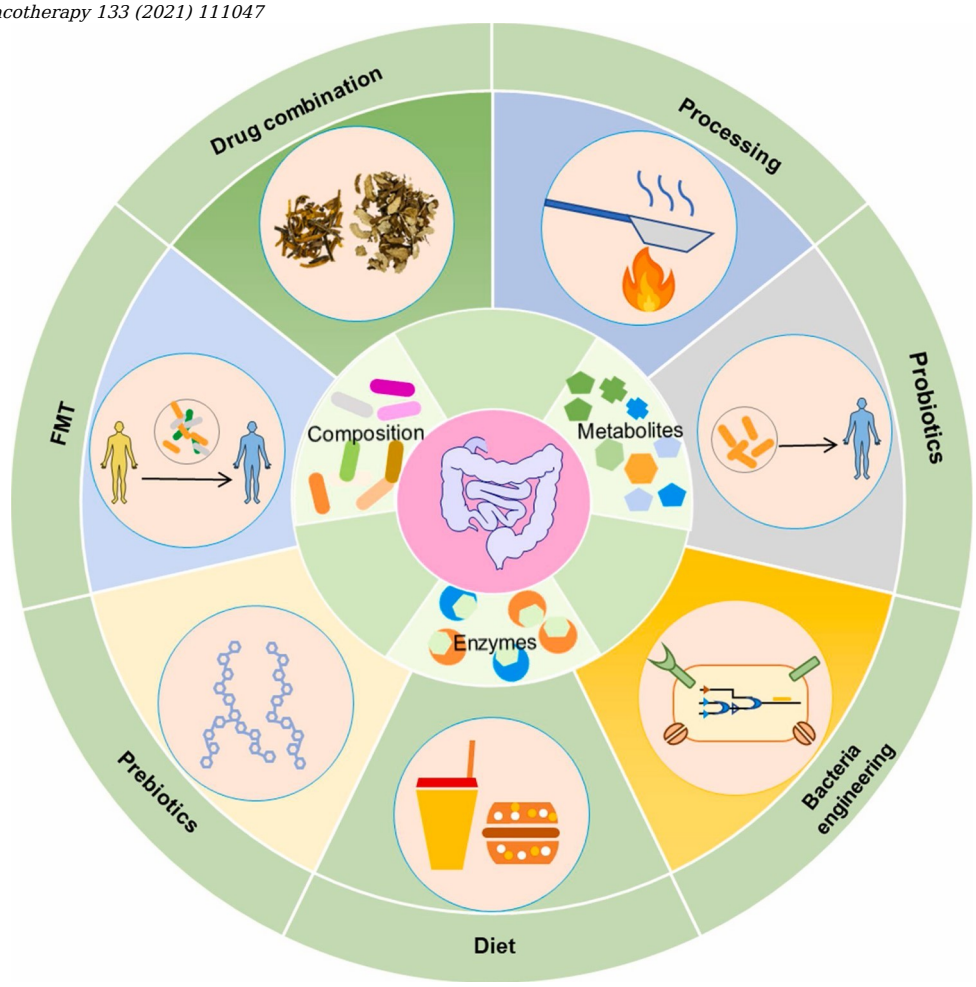

Fig. 2. The methods of manipulating gut microbiota to reduce the toxicity of TCMs. These methods can modulate the composition, metabolites and enzymes of gut microbiota and finally lead to toxicity modification of TCMs via mechanisms shown in Fig. 1.

Gansui significantly increased SCFAs level in comparison with Gansui group. Considering that the gut microbiota produced SCFAs exhibit anti-inflammatory and intestinal mucosa protecting effects [105], it can be deducted that processing with vinegar can modulate the composition and metabolism of gut microbiota and thus to reduce the toxicity of Gansui. However, because vinegar also belongs to SCFAs, further study is needed to the separate the contribution of processing and vinegar to the reduced toxic effects of Gansui.

6.2. TCMs combination

Combinational use of TCMs has been extensively practiced for thousands of years to avoid or reduce the toxicity of TCMs. Recent studies on gut microbiota have gradually revealed the toxicity reducing mechanism of the combination use of TCMs, as aforementioned Badou and Dazao [87]. The study on gut microbiota not only justified the rationality of conventional combinational use of TCMs, but also provided opportunity to find new TCMs and TCM compounds that can be combined to reduce the toxicity of TCMs. For example, gut microbiota released *β*-glucuronidase is an important enzyme that can hydrolyze the glycosides in herbal medicines to aglycones, and this process can increase the toxicity of herbal compounds and drugs [106]. Recent studies on chemical drugs have indicated that combination of chemical drugs such as non-steroidal anti-inflammatory drugs and *β*-glucuronidase inhibitors can reduce the toxicity of chemical drugs [107,108]. Similarly, some TCM compounds such as baicalin can inhibit the activity of bacterial *β*-glucuronidase, and combination of it with chemical drugs such as CPT-11can reduce the toxicity of CPT-11 [109]. A bacterial metabolite of quercetin, 3,4-dihydroxy- phenylacetic acid, can reduce the liver injury induced by acetaminophen [110]. Therefore, it can be deducted that the TCMs with the ability to inhibit bacterial enzymes with can be combined with other toxic TCMs or chemical drugs to reduce their toxicity.

6.3. Diet

It has been established that diet has an important influence on the composition and function of gut microbiota [111]. For example, diet rich in fiber can lead to significant shift of gut microbiota composition and increase of SCFAs production and is thus helpful for maintaining the normal function of innate and adaptive immune system [112]. On the contrary, low fiber intake can lead to decrease of SCFAs and is correlated with increased risk for disease including Crohn's disease, ulcerative colitis, chronic obstructive

pulmonary disease, obesity and diabetes [113,114]. Because of the important role of diet in modulation of gut microbiota composition and function, many studies have focused on manipulating diet to drug response. A typical example of this approach is the cardiac drug digoxin that is originally isolated from foxglove plant. Because digoxin has a very narrow therapeutic range, the dosage of it is great issue in clinical use. The gut microbiota can transform digoxin to cardio-inactive dihydrodigoxin. This transformation is substantial high in about 10 % patients and can lead to inactivation of more than 50 % of administered digoxin [49,52]. Using transcriptional profiling, comparative genomics, and culture-based assays, Haiser et al. demonstrated that *Eggerthella lenta* carrying "cardiac glycoside reductase" (cgr) operon is responsible for the inactivation of digoxin, and amino acid arginine can prevent the expression and activity of *cgr* [51]. In addition, the gnotobiotic mice receiving a high-protein diet (arginine rich diet) and colonized with *cgr* expressing *E. lenta* showed higher serum and urinary digoxin level in comparison with control groups. The study suggested that high-protein diet can suppress the digoxin inactivation and be adopted to reduce the toxic risk of digoxin in patients that originally require higher dosage. The example of digoxin highlights the potential of dietary intervention to reduce the toxicity of TCMs.

6.4. Others

Beyond the area of TCMs, other methods including fecal microbiota transplantation (FMT), supplement of prebiotics and probiotics and engineering of gut microbiota have the potential to reduce the toxicity of drugs [18]. For example, FMT can significantly ameliorate the refractory immune checkpoint inhibitors-induced colitis [115]. FMT can also significantly ameliorate FOLFOX (a regimen containing 5-fluorouracil, leucovorin and oxaliplatin)-induced intestinal mucositis and diarrhea in animal model of colorectal cancer [116]. Preventive administration of a probiotic strain *Lactobacillus casei* variety *rhamnosus* significantly reduced FOLFOX-induced intestinal mucositis and diarrhea in animal model of colorectal cancer while not changing the anti-tumor effect of FOLFOX [117]. Combination of TGF-*β* blockade and *Escherichia coli* Nissle 1917 enhanced tumor suppression effect of Galunisertib [118]. Engineering of gut microbiota is an emerging frontier to directly treat the disease and improve the drug outcome such as phenylketonuria and *L*-dopa [119]. Although those methods have not been applied to manipulate the toxicity of TCMs, it can be envisioned that those methods will be introduced to improve the outcomes of TCMs in the near future.

7. Manipulating gut microbiota to reduce the toxicity of contaminants

The best way to avoid the toxicity of contaminants is of course to ensure the quality of TCMs. However, this approach may meet great challenge because some contaminants such as heavy metal arsenic and mercury are also the active compounds of some TCMs. Thus, one ideal approach is to reduce the *in vivo* toxicity of contaminants while not removing the contaminants. Even though there are many cases showing that gut microbiota can exacerbate the toxicity of contaminants in TCMs, there is still a hope to manipulate the toxicity of them to reduce the toxicity of TCMs. For example, in a real-world based study, a probiotic containing *Lactobacillus rhamnosus* GR-1 reduced the blood levels of arsenic and mercury in pregnant women [120]. Similarly, separate supplementation with lead-intolerant bacteria including *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, and *Oscillibacter ruminantium* can protect against the toxicity of lead in mice [121]. In another study, the gut toxicity of patulin can be diminished by docosahexaenoic acid and supplementation of probiotic *Lactobacillus plantarum* CCFM8610 [93]. Other studies also showed the toxicity-reducing effects of probiotics [122,123]. These studies suggested that supplement with probiotics can be a good way to reduce the toxicity of contaminants in TCMs, although the outcome of this approach needs to be further studied. In addition to supplement with probiotics, control of diet can be used to reduce the toxicity of contaminants. For example, wheat bran intake can reduce the toxicity of cadmium via modulation of gut microbiota [124]. Worth notice is that although manipulating gut microbiota can be used to reduce the toxicity of contaminants, the strict quality control of TCMs is still needed to guarantee the safety of TCMs.

8. Perspectives

Now, we have understood the roles and mechanisms of gut microbiota in modification of the toxicity of TCMs. However, there is still a hug gap between knowing of the knowledge and utilization of the knowledge. There are several aspects should be noticed to propel the transformation of the knowledge into clinical practice. First, more studies should be carried to validate the relationship between gut microbiota and the toxicity of TCMs, including clinical, *in vitro*, and *in vivo* studies. This is because most of the current studies over the toxic modification of TCMs are carried only on animals and the studies rely on animals might not truly reflect the clinical outcome. In addition, in many cases, the causal or associative relationship between gut microbiota and toxicity of TCM has not been determined, especially the studies on TCM formulae. For example, even though current studies have indicated that gut microbiota is involved in the toxicity modification effects of compatibility [86,87], the casual relationship among gut microbiota, gut microbiota metabolites, gut microbiota transformed TCM compounds, and the toxicity of TCM needs to be investigated. Once the casual relationship has been established, the mechanism behind the toxicity-modification effects of gut microbiota can be revealed.

Second, methodologically, integrative approach should be used to predict the final toxicity of TCMs on human bodies. Current studies on single compounds from TCMs have greatly promoted our understanding of the toxicity of TCMs. However,

different from chemical drugs that one drug usually contains one bioactive compound, the typical feature of TCMs is that a TCM is usually composed of multiple compounds acting symmetrically [125]. Thus, the toxicity of one compound does not reflect the toxicity of a formula. And correspondingly, integration of the toxicity of multiple TCM compounds is needed to evaluate the toxicity of TCMs. In addition, the toxicity of drugs is influenced by both gut microbiota and hosts. For example, the toxicity of CPT-11 can be in influenced by hosts' gene variants UGT1A1*28, UGT1A7 N129 K/R131 K, and UGT1A7− 57 T/G in addition to gut microbiota [126]. Thus, integration of the effects of gut microbiota and hosts is needed to evaluate the final toxicity of TCMs.

Third, novel drugs with less toxicity can be mined from gastrointestinal tract. Gut microbiota synthesizes numerous natural products enabling microbe-microbe communication and microbial regulation of hosts' immune and metabolomic system, such as ruminococcin A, plantaricins, tryptamine, polysaccharide A [127,128]. Currently, a burgeoning area of gut microbiota is direct mining of those molecules with powerful bioactivities and transform those molecules into new drugs [129,130]. Bringing this approach to the area of TCM may beget a new area for developing TCM-based drug innovation. In general, two types of molecules can be developed as new drugs: the gut microbiota transformed TCM compounds, and the compounds synthesized *de novo* by gut microbiota. In addition to better efficacy and less toxicity, there are several other advantages of the drugs mined from gastrointestinal tract over conventional drugs, including higher bioavailability and less interindividual variation of drug response. This is because gut microbiota mainly conducts hydrolytic and reductive reactions that yield new metabolites with lower polarity and molecular weight [131]. Meanwhile, the drugs mined from gastrointestinal tract can be resistance to the metabolism of gut microbiota, and thus avoid the variation of drug response caused by gut microbiota.

Fourth, hormesis has emerged as an important concept to understand the pharmacology and toxicity of drugs and herbal compounds in recent years [132,133]. As a term used by toxicologists, hormesis refers to a biphasic dose response to a chemical agent that is characterized by stimulation or beneficial effect at a low dose and inhibitory or toxic effect at a high dose [134]. Recent studies have demonstrated that herbal compounds and mushrooms exhibit hormesis while treating Parkinson's-like phenotypes, Parkinson's disease, Meniere's disease and other diseases [135–140]. Studies have also showed obvious hormesis in TCMs [141] and combining the concept of Yin/Yang doctrine and hormesis has become a new frontier to understand the dose–response relationship in toxicology and pharmacology of TCMs [142]. Considering the importance of gut microbiota in modification of toxicity and efficacy of TCMs, combining gut microbiota and the concept of hormesis an interesting area that needs to be studied to understand the toxicity of TCMs.

Author contributions

C.P. conceived and proposed the idea; W.F. designed, wrote and revised the manuscript; J.L., Y.Z.T. and L.H.H. revised the manuscript. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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